

REMARKS

As the Examiner will note, claims 1, 3-5, 7 and 12-14 have been amended and accordingly claims 1, 3-5 and 7-14 are presently under consideration in the present application.

The Rejections

Claim 1 has been rejected by the Examiner under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. Claims 1, 3-5 and 7-14 have been rejected by the Examiner under 35 USC 103(a) as being unpatentable over Seo et al. (WO 03/033593), in view of Sodergard (US 2004/0091573) in view of Li et al. (Polymer, 39, pp. 4421-4427 (1998)). These rejections are respectfully traversed.

The Invention

The present invention as amended relates to a micellar composition comprising a water-soluble polylactic acid derivative which can form stable micelles and increase the solubility of poorly water-soluble drugs by entrapping the drugs in micelles. The present invention stabilizes micelles by increasing the molecular weight of the polymer which is used to form the micelles and accordingly lowering the critical micelle concentration (CMC). If CMC is too high, more polymer is required to form micelles and then the micelles become unstable, which results in precipitation of poorly water-soluble drugs. If the molecular weight of a linear PLA salt increases, it becomes more difficult to dissolve in water. The present inventors have designed a multiarm polymer structure wherein the total molecular weight increases but that of each PLA arm does not, while the water solubility is maintained.

The Prior Art

The Seo reference does not provide any teaching or suggestion as to whether the molecular weight of a linear PLA salt should increase, how to increase the molecular weight, and whether the water solubility would be maintained and micelles could be formed even if the molecular weight increases.

The Li reference relates to conversion of a linear ABA triblock copolymer to a star-block PLLG-PEO copolymer having steric architecture and a shorter PLLG block. The purpose of the Li reference is to deliver proteins. The polymer of the Li reference, which is not dissolved in water, is a block copolymer comprising PEG. Therefore, it is clearly distinguishable from the present polylactic acid derivatives. Furthermore, the Li reference provides no teaching or suggestion on how to maintain the water solubility of a polymer even if its molecular weight increases. Li does not pertain to entrapping poorly water-soluble drugs in micelles.

The Sodergard reference relates to a chewing gum. In the Sodergard reference, biodegradable polymers are used as a gum base. That is, the technical field of the Sodergard reference is totally different from that of the present invention, i.e., drug delivery. In the Sodergard reference, it is not necessary for the polymer to entrap drugs therein at all. In addition, the polymer of the Sodergard reference is used for a gum base and thus should not be water soluble. One skilled in the art would never refer to the teachings of the Sodergard reference for developing a drug-delivery system.

The Examiner argues that the Sodergard reference was used as a secondary reference for its description on how to make PLA multiarm copolymers and not for its description of how to use such polymers (page 5 of the Office Action). However, the technical field of the Sodergard reference and the use of polymers prepared by the Sodergard reference are totally different from those of the present invention. Thus, the Sodergard reference would not be relevant for a skilled artisan to consider for developing a drug-delivery system. Furthermore, the Sodergard reference provides no teaching or suggestion concerning the use of polymers as drug delivery agents for forming stable micelles. Thus, it is unlikely that the combination of the Sodergard polymer with the teachings of the Seo and Li references would be tried at all since the technical fields of the inventions are totally different. Furthermore, even if they were combined, such a combination provides no prediction, teaching, suggestion or motivation as to whether the molecular weight of the PLA salt should increase in order to increase micelle stability and whether the water

solubility would be maintained and micelles could be formed even if the polymer is prepared in a multiarm form.

The Examiner alleges that from Li's disclosure, a multiarm form is more advantageous than a linear form in drug delivery and thus the incorporation of Seo's PLA into Sodergard would be obvious to one skilled in the art. However, Li's teaching is that in a PEG-PLA block copolymer, a star-block copolymer has a lower Tg and crystallinity and thereby a low degradation rate, as compared with a linear form. Li explains that this is because of slower cleavage of the PEG-PLL bond (conclusion of Li). That is, Li's teaching is not that a multiarm form is better than a linear form for drug delivery in all properties but that in block copolymers containing PEG, higher molecular weight makes its degradation slower. Such a teaching has no relation to an increase of micelle stability and drug solubility which are important factors in a drug delivery system. The slow degradation of high Mw polymers (by slower cleavage of the polymer bond) has no relationship to the increase of micelle stability (by lowering CMC). Therefore, Li provides no motivation by which a skilled artisan would employ multiarm polymers in a drug delivery system to stabilize micelles.

According to Experimental Example 1 of the present application, the branched polymer of the present invention can form micelles even when its molecular weight increases. Furthermore, according to Experimental Example 2 of the present invention, comparing PLA-COONa (1,140; 10% of drug) with 3-arm PLA-COONa (3,000; 10% of drug), the drug solubility increased from 20 to 27 mg/ml, which corresponds to a 35% increase in solubility. Such a remarkable effect of the present invention (i.e., increasing drug solubility as well as micelle stability) would not be expected from any of Seo and Li or their combinations.

Lee discloses a molecular weight of 33,200 for its polymer (pages 978 and 983). Such a high molecular weight is far beyond the scope of the present polymer and is neither water soluble nor capable of forming micelles. Lee relates to a drug delivery for water-insoluble materials wherein the degradation rate, depending on terminal groups, is important. Lee does not pertain

to the technical idea of forming stable micelles and entrapping poorly water-soluble drugs therein.

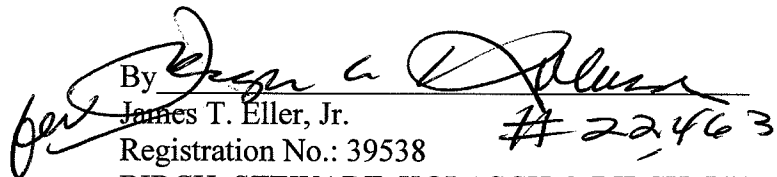
Accordingly, in view of the above amendments and remarks reconsideration of the rejections and allowance of all of the claims of the present application are respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Joseph A. Kolasch, Registration No. 22463 at the telephone number of the undersigned below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

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Respectfully submitted,

By 
James T. Eller, Jr.
Registration No.: 39538 #22,463
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road, Suite 100 East
P.O. Box 747
Falls Church, VA 22040-0747
703-205-8000

**JOSEPH A. KOLASCH
REG. NO. 22,463**